CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER for: 020779, S022

MEDICAL REVIEW(S)

In addition, please submit three copies of the introductory promotional materials that you propose to use for these products. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you of your responsibility to comply with the requirements of 21 CFR 314.510 as indicated in the approval letter dated March 14, 1997.

We also remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Sylvia D. Lynche, Pharm.D., Regulatory Management Officer, at (301) 827-2335.

Sincerely,

/S/

Heidi M. Jolson, M.D., M.P.H.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Medical Officer Review
Of
Supplemental NDA 20,778 and 20,779, SE2
For
Interim Study Report of AG1343-542:
A Phase III Study Comparing BID and TID Dosing of VIRACEPT™
In Combination with Stavudine (d4T) + Lamivudine (3TC)
In HIV-Positive Patients

Date Submitted:	01/26/99
Date Completed:	11/12/99
Reviewer:	Teresa C. Wu, M.D., Ph.D.
Applicant:	Agouron Pharmaceuticals, Inc. 10350 North Torrey Pines Road La Jolla, CA 92037-1022 (619) 622-8807
Drug:	VIRACEPT™ (nelfinavir mesylate)
Dosage/Formulation and Administration:	Tablet (250-mg strength), oral
Recommended Dosage:	1250 mg b.i.d. or 750 mg t.i.d. with meal/light snack
Approved Indication:	Treatment of HIV-1 Infection

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1. Materials Reviewed

This submission consists of an archival copy of 26 volumes. In addition, the applicant provided the SAS data transport files on CD Rom and a draft labeling on disk.

2. Regulatory Background

In March of 1997, VIRACEPT®, an inhibitor of HIV-1 protease, received accelerated approval for treatment of HIV infection based on 3 studies: AG1343-505, AG1343-511, and AG1343-506 (henceforth referred to as study 505, 511, and 506). Study 505 was a monotherapy study, Study 511 and 506 were both combination studies. The approval was based on results of changes in surrogate markers in controlled studies of up to 24 weeks of duration.

In order to improve patient acceptance and compliance, the applicant conducted study AG1353-542 (henceforth referred to as study 542) to determine whether a twice a day dosing regimen of Viracept, in combination with d4T and 3TC, would provide similar safety and efficacy compared to a three times daily dosing regimen of Viracept.

This submission contains the applicant's interim report of study 542. The study is ongoing.

3. Synopsis: AG1343-542
Title: **A phase 3 study comparing BID and TID Dosing of VIRACEPT in combination with stavudine (d4T) + lamivudine (3TC) in HIV-positive patients**

This study has been conducted at 21 centers in Europe.

Some important event dates are listed below:

Date of first enrollment:	3/11/97
Date of data cutoff:	7/31/98
Date of interim report submission:	1/11/99
Date of additional analysis:	8/20/99

3.1 Study Design

This randomized phase 3 study originally was designed to compare the efficacy and safety of 4 different dose levels (750 mg BID, 1000 mg BID, 1250 mg BID, or 750 mg TID) of Viracept in combination with d4T 40 mg BID and 3TC 150 mg BID. The initial study design intended to enroll 240 patients (60 patients per group). The three BID dose groups were blinded. The study was later changed to an open-label, two dose-group comparison design as a result of the following amendment:

Amendment 1 (09/18/97)

- Because results from study 511 demonstrated a clear advantage of the 750 mg TID group over the 500 mg TID group with respect to durability of response, the protocol was amended to re-allocate all patients randomized to the 750 mg BID or 1000 mg BID group to receive 1250 mg BID. As a result, the study became an open-label, two group comparative trial of two dose regimens: 1250 mg BID vs. 750 mg TID for a treatment duration of 48 weeks in 360 patients.

Additional amendments provided below were made to the study design:

- Initially, the primary efficacy variable was 'log reduction in HIV RNA level'. (In this review, HIV RNA level denotes HIV-1 RNA level.) This variable was subsequently amended to 'percentage of patients with plasma HIV RNA levels below the limit of assay quantification (LOQ)'. The primary efficacy endpoint was further specified as durability of viral load reduction, as measured by the percent of patients with plasma HIV RNA levels below the LOQ at Weeks 24 and 48. In the interim report, both the 'percentage' and 'durability' parameters were analyzed.

- Initially, HIV RNA was measured by using the [redacted] assay which had a lower limit of quantification of 500 copies/ml. All stored backup plasma samples collected before July 1977 which had been assayed by the [redacted] method were re-assayed for HIV RNA levels by the [redacted] Assay with a lower limit of quantification of 400 copies/ml. Samples with HIV RNA levels that fell below 400 copies/ml for the standard PCR assay were further measured using the UltraSensitive PCR method with a lower limit of quantification of 50 copies/ml.

  Comment: In March of 1999, the [redacted] Test for both the Standard and UltraSensitive specimen processing procedures was approved for marketing for assessing patient prognosis and monitoring the effects of antiretroviral therapy.

3.2 Patient Selection Criteria

Eligibility criteria were: men and women, HIV positive and 13 years of age or older; had a quantitative plasma HIV RNA level of $\geq$ 15,000 copies/ml; had received < 6 months of nucleoside therapy; had received a protease inhibitor for <2 weeks, were both d4T and 3TC-naïve before Amendment 1; subsequent to Amendment 1, patients had to be naïve to 3TC only.

3.3 Randomization and Treatment Assignment

Patients were randomized to one of the two following treatment groups:

- Viracept 1250 mg BID (5 tablets/dose, with food)

- Viracept 750 mg TID (3 tablets/dose, with food)

Treatment groups were to be balanced according to CD4 cell counts (<200 cell/mm3 or ≥200 cell/mm3).

All patients were to receive d4T at 40 mg BID and 3TC at 150 mg BID.

3.4 Patient Evaluation Schedule

Assessments were performed at Screen 1; Screen 2 (day –7); Baseline (day 0); Weeks 4, 8, 12, 16, 24, 32, 40, and 48; every 12 weeks thereafter until the last patient reached Week 48; and 1 month after the end of treatment.

The HIV RNA assays were performed from plasma collected from each scheduled visit. CD4/CD8 counts were performed during each scheduled visit beginning from Screen 2. Plasma samples for full pk profiles were collected only at selected sites after the morning dose on Week 4 at predose, 1, 2, 3, 4, 5, 6, and 8 hours postdose for the TID and BID groups and at 10 and 12 hours postdose for the BID groups.

3.5 Sample Size Considerations

The planned sample size was initially 60 patients per treatment group and was based on demonstrating equivalence between the BID and TID dose regimens with respect to average change from baseline in $\log_{10}$ HIV RNA. Subsequently, the sample size was amended to 180 randomized patients (compared to the original 60 patients per treatment group) in the VIRACEPT 1250 mg BID and 750 TID groups in order to demonstrate equivalence between these 2 dose regimens with respect to the proportion of patients with plasma HIV RNA levels below the LOQ at 48 weeks. Thus, an additional 120 per group were to be enrolled after the study was amended. Assuming a 20% attrition rate, the sample size of 180 patients in each treatment group was expected to provide complete data on 142 patients in each group at Week 48. This sample size was calculated based on a 0.05 two-sided test with 80% power, assuming a delta of 10%. This 10% delta was consistent with FDA's recommendation for the purpose of sample size estimation (Please refer to a correspondence issued by the division dated 10/24/97.)

3.6 Drug Accountability

The investigator or designee had the responsibility to determine Viracept accountability. If any Viracept supplies could not be accounted for, an explanation signed by the investigator was required.

Supplies of d4T and 3TC were obtained by the site as commercial products. There was no procedure specified in the protocol for monitoring patients' compliance with these two drugs.

3.7 Dose Modifications for Study Drugs Related Toxicity

Patients experiencing Grade 3 or 4 Viracept related toxicity (except diarrhea) were, at the discretion of the investigator, to have their daily dose of Viracept temporarily halted or discontinued. Likewise, dose modifications were considered for all Grade 3 or 4 toxicities most likely attributable to d4T and 3TC. If discontinuation was recommended, another nucleoside agent could be administered, after consultation with the Agouron Medical Monitor.

3.8 Definition of Treatment Failure

Treatment failure was defined as a three-fold increase in viral load from the patient's lowest value and a viral load increase to $\geq$10,000 copies/ml. This increase must have been documented over two consecutive visits.

3.9 Analysis of Primary Efficacy Variables (Agouron vs. FDA)

There were two primary efficacy variables:

- Percent of patients with HIV RNA <LOQ at Weeks 24 and 48
- Duration of suppression (<LOQ), i.e. time to failure

A. Percent of Patients with HIV RNA below the LOQ at Weeks 24 and 48 (**Agouron**)

The applicant computed the percent of patients with HIV RNA <LOQ using the following 3 different approaches for dealing with missing values:

- Intent-to-treat analysis: noncompleters assumed as Failure (ITT, NC=F)
  1. A missing data point was replaced by a failure if either the preceding or succeeding result was a failure or missing.
  2. If both the preceding and succeeding results were successes, the data point remained as missing, i.e., no data were imputed.
  3. If a patient prematurely discontinued and had no follow-up data, the patient was classified as a failure at all subsequent timepoints. However, the patient who discontinued was assumed as a failure only up to the timepoint that he or she could have completed if he or she had been still in the study. For example, if a patient started the study on 04/06/98 and discontinued from the study on 06/01/98, the patient was on study for 8 weeks. If the patient had still been in the study, he or she could only have been on study for a maximum of 16 weeks up to the data cutoff date, 07/31/98. Therefore, the patient would be assumed as a failure after week 8 but only up to week 16, and be excluded from week 24 through week 48.

- Intent-to-treat: last observation carried forward (LOCF)
  For each patient, the last available on-treatment result was used as the endpoint for the patient.

- On-treatment analysis:
  At a specific timepoint, the percent of patients with plasma HIV RNA levels below LOQ was calculated as the number of patients below LOQ divided by the number of patients with plasma HIV RNA levels results at the timepoint. That is, no data were imputed.

B. Duration of Suppression (<LOQ) in Plasma HIV RNA Levels (**Agouron**)

The analysis of duration of suppression was based on Kaplan-Meier estimates using the following algorithm:

- Virologic response was defined as 2 consecutive HIV RNA measurements below LOQ.
- Virologic relapse was defined as 2 consecutive HIV RNA measurements above LOQ after a virologic response.
- Duration of response was defined as interval from the first visit the patient qualified as a responder to the first of the virologic failure qualifying visits.

C. Percent of patients <LOQ and duration of suppression (**FDA**)

(For more details, please refer to Dr. Tom Hammerstrom's statistical review.)

Both variables were analyzed based on Kaplan-Meier estimates using the following algorithm:

- Time to virological failure = 0, if the patient failed to achieve HIV RNA levels <LOQ while on the original assigned treatment arm (i.e. BID or TID).
- If the patient achieved <LOQ while on the original assigned treatment arm, then the time to virological failure = the earliest of the events listed below:
  (1) switched to different treatment
  (2) dropped out of study
  (3) achieved LOQ but subsequently had a confirmed rise about 400 copies/ml
  (4) reached a CDC Category C event.

3.10 Secondary Efficacy Variable: CD4 Lymphocyte Count

The mean changes from baseline in absolute CD4 lymphocyte counts for patients treated with Viracept BID and TID dose regimens were compared.

4. Results

4.1 Patient Disposition

Since the protocol had been amended from 4 treatment groups to 2 treatment groups, the applicant designated patient enrollments as Cohorts 1 and 2 which are defined as below:

- Cohort 1: patients enrolled in the original protocol. The majority of patients initially randomized to 750 mg (n=68) and 1000 mg (n=71) were switched to the 1250 mg BID by week 24 and all had switched before week 40 (n=286).
- Cohort 2: Patient enrolled after the study design was amended (n=173).

Of the 459 (286+173) patients randomized, 299 patients were randomized to a BID regimen of nelfinavir and 160 were randomized to the TID regimen. Since there were 4 patients who did not received treatment (no study drug dispensed or withdrew consent), the remaining 455 patients (296 BID, 159 TID) were included in safety analyses. Of these patients, 447 (291 BID, 156 TID) were included in efficacy analyses; 8 patients were excluded from efficacy analyses because they had no on-treatment efficacy evaluations.

4.2 Demographic and Baseline Characteristics

Patients' demographic and baseline characteristics are presented in Table 1.

Table 1: Demographic and Baseline Characteristics

Variable	1250 mg BID (n=296)	750 mg TID(n=159)
Gender, n (%)		
Male	265 (86.5)	128 (80.5)
Female	40 (13.5)	31 (19.5)
Race, n (%)		
Caucasian	269 (90.9)	143 (89.9)
African American	22 (7.4)	12 (7.5)
Asian	5 (1.0)	2 (1.3)
Other	2 (0.6)	2 (1.3)
Age (yrs)		
Mean (SD)	36.2 (9.8)	36.7 (10.6)
Range	18-70	20-83
Weight (kg)		
Mean (SD)	70.2 (11.5)	69.5 (11.2)
Range	45-105	42-100
HIV duration (month)		
Mean (SD)	**38.7 (43.7)**	**29 (37)**
Range	0.4-182	0.7-160.9
Karnofsky scores		
Mean (SD)	95.1 (6.3)	93.8 (6.5)
Range	70-100	70-100
Baseline CD4, cells/mm3[1]		
Mean (SD)	278.5 (188)	283.8 (201.7)
Range	10-972	10-983
Baseline HIV RNA, log_{10} of copies/ml [1]		
Mean (SD)	5.0 (0.5)	5.1 (0.5)
Range	3.3 –6.6	4.0-6.4

Source:Table 6, vol.18, page 76

With the exception of the duration of time since HIV diagnosis, there were no clinically relevant differences in demographic or baseline characteristics between the BID and TID groups. The mean time since HIV diagnosis was longer in

[1] Calculated baseline value: by averaging the latest 2 results that were taken prior to the initiation of nelfinavir and were within 30 days before the start of study medication.

patients receiving the BID treatment than the TID treatment: 38.7 months vs. 29 months.

4.3 Patient Discontinuations

As of the data cutoff date, 72 patients (72/455, 16%) discontinued the study. The percentage of patients who discontinued was similar in patients receiving Viracept BID and those receiving the TID regimen (16.5% and 14.4% respectively). The following table lists the reasons for study discontinuation.

Table 2: Patient Discontinuations

Reason (n)	Relation to study drug	BID regimen N=296	TID regimen N=159
Patient request (16)	No	10	6
Treatment failure, per protocol (12)	NA	8	4
Intercurrent illness (10)	No	9	1
Loss to follow-up(7)	No	4	3
Nelfinavir toxicity(8)	Yes	6	2
Noncompliance(4)	No	2	2
Antiretroviral agents (other than Viracept) toxicity (4)	No	3	1
Other * (11)	No	7	4
Total	NA	**49(16.5%)**	**23(14.4%)**

* increase in viral load; treatment failure not meeting protocol definition; death

(Source: Vol. 18, p. 74, Table 5)

4.4 Patient Medication Compliance

Overall, as based on the number of missed doses of Viracept, patients receiving either the BID or TID treatment were generally compliant. Patients who received the BID treatment maintained closer adherence to their prescribed dose regimen than patients who received the TID treatment. The mean number of missed doses was 14 for patients receiving the BID treatment and 28 for patients receiving the TID treatment.

4.5 Antiretroviral Treatment Changes

A similar proportion of patients receiving Viracept BID (53 patients, **18%**) and TID (24 patients, **15%**) treatment had changes in concomitant antiretroviral treatment (dose reduction or discontinuation or interruption of treatment) during the study. For patients who had antiretroviral treatment changes, the median time until the first treatment change was longer in patients receiving the BID treatment compared with those receiving the TID treatment (115 days and 72 days, respectively)

4.6 Protocol Violations

There were no on-study protocol violations. A total of 31 (7%) of the 455

patients who were randomized and treated had violations of eligibility criteria; 17 (**6%**) of 296 patients who received the BID treatment and 14(**9%**) of 159 patients who received the TID regimen. The most common violation was use of an immune modulator or vaccine within 1 month before Day 0. All eligibility violations were exempted with the applicant's approval.

4.7 Applicant's Efficacy Analyses –Percent of Patients with HIV RNA below the LOQ

A total of 447 patients were evaluable for efficacy analyses. Eight patients were excluded from efficacy analyses because they had no on-treatment efficacy evaluations. The efficacy analyses included all patients randomized to the study who received at least 1 dose of Viracept and had at least 1 efficacy measurement after Baseline (day 0).

Because the conclusions made by the applicant with the ITT/NC=F, LOCF, and On-Treatment analyses were the same, only results of ITT/ NC=F analysis are presented in this MOR.

Analyses using the standard PCR assay and the UltraSenstive PCR assay will be presented separately.

4.7.1 Results by the Standard PCR Assay

The following Table and Figure present the proportion of patients on each regimen who had plasma HIV RNA levels below 400 copies/ml.

Table 3: Intent-to-Treat Analysis (NC=F), Standard PCR Assay

Study Visit	VIRACEPT 1250 mg BID* n/N (%)	VIRACEPT 750 mg TID n/N (%)	Pairwise Comparison BID-TID	95% CI
Week 4	70/291 (24.1)	28/156 (17.9)	6.1	(-1.7, 13.9)
Week 8	173/277 (62.5)	65/145 (44.8)	17.6	(7.7, 27.5)
Week 12	198/265 (74.7)	85/128 (66.4)	8.3	(-1.4, 18.0)
Week 16	203/255 (79.6)	92/117 (78.6)	1.0	(-7.9, 9.9)
Week 24	180/240 (75.0)	84/108 (77.8)	-2.8	(-12.3, 6.8)
Week 32	152/215 (70.7)	55/ 80 (68.8)	1.9	(-9.9, 13.8)
Week 40	134/199 (67.3)	53/ 75 (70.7)	-3.3	(-15.5, 8.9)
Week 48	131/204 (64.2)	48/ 75 (64.0)	0.2	(-12.5, 12.9)

Abstracted from Statistical Table A.13 and Data Listing A.10. Vol 3

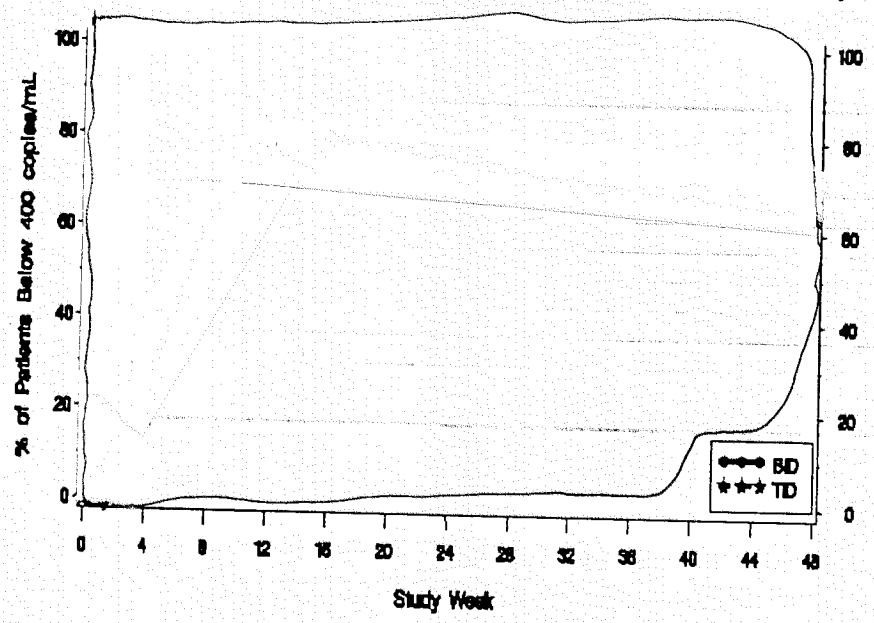
* The majority of patients were receiving 1250 mg BID by Week 24 and all were receiving 1250 mg BID before Week 40. Vol 3

CI=confidence interval.

NC=F=Noncompleters assumed as failures.

Source: vol.18, page 81.

Figure 1: Intent-to-Treat Analysis: NC=F, Standard PCR Assay



Source: vol. 018, Page 82.

At Week 24, a decrease in plasma HIV RNA level to below 400 copies/ml was observed in 75% of patients who received the BID regimen and 78% of patients who received the TID regimen when noncompleters were considered failures. This level of suppression was present at week 48 for 64% patients on each regimen. The lower limits of the 95% CI on the difference in percent of patients with plasma HIV RNA levels below 400 copies/ml between the 2 dosing regimens (BID minus TID) were **–12.3%** at Week 24 and **–12.5%** at Week 48.

4.7.2 Results by the UltraSensitive PCR Assay

The following Table and Figure present the proportion of patients on each regimen who had plasma HIV RNA levels below 50 copies/ml as measured by the UltraSensitive PCR assay.

Table 4:Intent-to-Treat Analysis:NC=F, UltraSensitive PCR Assay

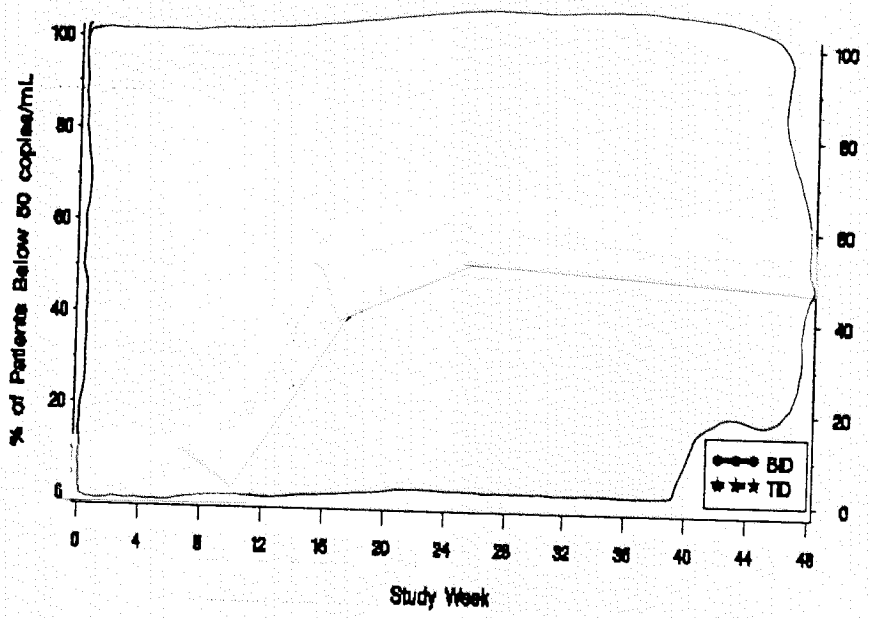
Study Visit	VIRACEPT 1250 mg BID* n/N (%)	VIRACEPT 750 mg TID n/N (%)	Pairwise Comparison BID–TID	95% CI
Week 4	5/291 (1.7)	2/156 (1.3)	0.4	(–1.9, 2.7)
Week 8	29/277 (10.5)	10/145 (6.9)	3.6	(–1.9, 9.1)
Week 12	61/268 (22.8)	28/130 (21.5)	1.2	(–7.4, 9.9)
Week 16	130/259 (50.2)	44/120 (36.7)	13.5	(3.0, 24.1)
Week 24	145/241 (60.2)	59/108 (54.6)	5.5	(–5.7, 16.8)
Week 32	122/215 (56.7)	47/80 (58.8)	–2.0	(–14.7, 10.7)
Week 40	109/201 (54.2)	39/75 (52.0)	2.2	(–11.0, 15.5)
Week 48	111/204 (54.4)	38/75 (50.7)	3.7	(–9.5, 17.0)

Abstracted from Statistical Table A.14 and Data Listing A.10.

* The majority of patients were receiving 1250 mg BID by Week 24 and all were receiving 1250 mg BID before Week 40.

CI= confidence interval.

Figure 2: Intent-to-Treat Analysis: NC=F, UltraSensitive PCR Assay



Source: vol. 18, page 84.

For the ultrasensitive PCR assay, 60% of patients who received the BID regimen and 55% of patients who received the TID regimen had plasma HIV RNA levels below 50 copies/ml at Week 24. This level of suppression was present at Week 48 for 54% and 51% of patients in the BID and TID regimens, respectively. The lower limits of the 95% CI on the difference in percent of patients with plasma HIV RNA levels below 50 copies /ml between the 2 dose regimens (BID minus TID) were **–5.7**% and **–9.5**% at Weeks 24 and 48 respectively.

4.8 FDA's Analyses: Percent of Patients with HIV RNA below the LOQ

A Kaplan-Meier based approach was used by Dr. Hammerstrom. He applied the algorithm described previously under Section 3.9 of this review.

Dr. Hammerstrom pointed out that, as of the data cutoff date, 11% (35/304) and 16% (27/167) of subjects in the BID and TID regimens, respectively, were administratively censored before reaching week 12 on treatment. These early censored patients, without ever reaching <LOQ of HIV RNA, were counted as failures in the applicant's analysis. In order to examine the sensitivity of the conclusions made by the applicant relating to classifying such patients as failures, Dr. Hammerstrom carried out two analyses in which these subjects were either 1) counted as failures at time zero, or 2) counted as missing data and excluded from the analysis.

Dr. Hammerstrom also pointed out that the applicant's analyses did not reflect the type of stratification used in the randomization, i.e., baseline CD4 counts ≥ 200 cells/ml vs. < 200 cells/ml. Therefore, he computed separate Kaplan-Meier estimates for each of the baseline CD4 strata and then computed a pooled estimate using a Mantel-Haenszel weighting.

Results of Dr. Hammerstrom's analyses are shown in Table 5 and Table 6.

Table 5: Proportion of Subjects HIV RNA Levels <LOQ at Week 24

Assay Procedure	Proportion of Subject HIV RNA Levels <LOQ			
	Assumptions	Nelfinavir 1250 mg BID (n=304)*	Nelfinavir 750mg TID (n=167)*	95% CI BID-TID
Standard	<12 W =Failure	69%	69%	-9%, 8%
	<12 W excluded	77%	83%	-14%, 3%
	Stratified by site/CD4	78%	83%	-13%, 2%
UltraSensitive	<12 W =Failure	60%	52%	-1%, 18%
	<12 W excluded	69%	65%	-6%, 14%
	Stratified by site/CD4	70%	66%	-5%, 13%

*Numbers were based on the applicant's computer files.

Table 6: Proportion of Subjects HIV RNA Levels <LOQ at Week 48

Assay Procedure	Proportion of Subject HIV RNA Levels <LOQ			
	Assumptions	Nelfinavir 1250 mg BID (n=304)*	Nelfinavir 750mg TID (n=167)*	95% CI BID-TID
Standard	<12 W =Failure	57%	60%	-14%, 7%
	<12 W excluded	64%	72%	-19%, 3%
	Stratified by site/CD4	66%	75%	-18%, 1%
UltraSensitive	<12 W =Failure	44%	38%	-4%, 16%
	<12 W excluded	51%	48%	-9%, 15%
	Stratified by site/CD4	52%	52%	-10%, 10%

*Numbers based on computer files provided by the applicant.

When the standard PCR assay was used, the Viracept 1250 mg BID regimen was no more than 14% worse than the Viracept 750 mg TID regimen with respect to the proportion of subjects having HIV RNA levels <LOQ at week 24; and the BID regimen was no more than 19% worse than the TID regimen at week 48. Dr. Hammerstrom considered that this degree (14-19%) of uncertainty could be partially due to early censoring. When the study progresses to completion, the size of uncertainly is expected to decrease.

When the UltraSensitive assay was used, the degree of uncertainty is less pronounced. The lower limits of the 95% CI on the difference in percent of